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1 Three novel CFTR mutations found in Turkish patients with cystic fibrosis

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Cystic fibrosis is the most common fatal autosomal recessive multisystem disorder, which occurs mainly in European-derived populations. There are currently more than 1500 mutations. DF508, which is a deletion of the phenylalanine at position 508, is the most common mutation. The R347P is a rare missense mutation located within the first membrane spanning domain (MSD1) of the CFTR protein. This mutation occurs with an overall worldwide frequency of about 0.2%. L812X, 3608 ins G and 1853C mutations have not been reported yet in cystic fibrosis patients. Here; we report three Turkish children who were diagnosed to have cystic fibrosis based on characteristic manifestations of cystic fibrosis and pathological sweat test results. By the genetic analysis, in case 1, R347P mutation was identified in a compound heterozygote state with a novel mutation, L812X. In case 2 and 3, 3608 ins G and 1853C mutations were respectively determined.

2* Identification of two Alu insertions in the CFTR gene

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LINE-1 (long interspersed element-1) or L1-mediated retrotransposition is a potent force in human genome evolution and an occasional cause of human genetic disease. Since the first report of two de novo L1 insertions in the F8 gene causing hemophilia A, more than 50 L1-mediated retrotranspositional events have been identified as causing human genetic disease.

On the basis of the observation that both L1 elements and Alu sequences are abundant in the human genome, the increasing number of large genomic rearrangements reported in the CFTR gene, and the fairly large size of the CFTR gene, we surmised that some previously unresolved cystic fibrosis chromosomes might carry hitherto undetected L1-mediated retrotranspositional insertions.

This study therefore report the detection and the characterization of two simple Alu insertions using quantitative high-performance liquid chromatography (QHPLC), technique previously employed to delineate the boundaries of large genomic deletions in the CFTR gene.

The first one, identified in a 24-year-old French girl, carrying F508del on the other chromosome, corresponds to a 103 bp antisense insertion in exon 16 containing an Alu sequence of 46 bp and a poly(A) tail of 57 bp. The second one, identified in a 28-year-old Czech man with typical cystic fibrosis, correspond to a 337 bp sense insertion of an Alu sequence of 281 bp and a poly(A) tail of 56 bp. Both mutations are presumed to lead to aberrant splicing.

The identification of these two simple Alu insertions in the CFTR gene not only revealed a previously unknown mutational mechanism responsible for cystic fibrosis but also represents an important addition to the already diverse spectrum of CFTR gene mutations.

3* Spectrum of CFTR mutations in a group of black patients from South Africa: Identification of a novel large rearrangement

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CF is still thought of as a rare disease in black Africans with an estimated incidence of 1 in 12,000 to 1 in 15,000 and minimal information is available concerning the spectrum of CFTR mutations in this population. Extensive screening of 12 patients for CFTR mutations using DGGE and sequencing of abnormal patterns resulted in the detection of 62.5% of the molecular defects (3120+1G>A, p.Gly1249Glu, 2183delAA, 3196del54, –94G>T): 6 homozygous or compound heterozygous, 3 heterozygous and 3 without mutation.

Patients with unidentified alleles were subsequently tested for large rearrangements using a semi-quantitative fluorescent PCR assay. A deletion of exon 2 was found in a patient heterozygous for the most common mutation in this population (3120+1G>A). Mapping and sequencing the breakpoint junction revealed that the large deletion [c.54–1161_c.164+1603del2875] was different from the deletion of exon 2 [c.54–5811_c.164+2186del8108ins182] previously described in Caucasian patients. The mutational mechanism could be explained by a classical model of replication slippage due to direct repeats present at the 5' and 3' breakpoints. Unresolved alleles may have mutations in non-coding CFTR regions not investigated; however, the lack of mutation detection in 3 patients without consanguinity could result from the contribution of other gene(s) or to misdiagnosis due to false positive sweat test results that may be more common in some populations.

This study emphasizes the importance of scanning the entire CFTR gene and including a search for gross rearrangements in CF diagnosis.

4 Analysis of CFTR gene mutations in Moscow region

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The aim of our study was to describe a mutation spectrum of the CFTR gene in CF patients from Moscow region. At present day in Moscow centre of CF are registrated 178 patients (aged 2 months – 18 years) from Moscow and Moscow province. Genotypes were tested in 169 children with CF (including 5 patients on National program of newborn screening on CF, started in 2006). The median age of genetic diagnosis is 3.8 years (q25 = 1.0, q75 = 7.3).

DNA analysis on CFTR mutations in Russian Centre for Medical Genetics is performed routinely from 1990. Now it is possible to define 23 CFTR gene mutations, among which we found 14 mutations in Moscow region young patients (338 alleles): ΔF508 – 60.3%, CFTRdele2,3(21kb) 9.2%, W1282X 2.6%, 2143delTT 2.1%, N1303K 1.7%, G542X 1.7%, 3849+10kbC → T 1.5%, 2184insA 1.2%, 677delTA 0.6%, L138insA 0.6%, 604insA 0.6%, R334W 0.6%, 3821delT 0.3%, 394delTTex3 0.3%. 17.1% of CFTR alleles are not identified, this index is lower, than on the whole Russia (26.6%). Most probably, it is explained by a multi-ethnic society. In our days there is a necessity to expander the mutation panel, that will allow to create the «Slavic» panel on the one hand, and the multinational panel for different ethnic groups in Russia on the other hand. It will help to improve a quality of screening, especially in doubtful cases.